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SCIENCE DESK

2 New Methods to Sequence DNA Promise Vastly Lower Costs

By NICHOLAS WADE (NYT) 672 words
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A new way of decoding DNA, potentially far cheaper and quicker than the existing method, has been developed by researchers at the Harvard Medical School.

The Harvard team, led by Jay Shendure and George M. Church, describes the method in the current issue of *Science*. Last week, another new method for sequencing DNA was announced by a company in Branford, Conn., 454 Life Sciences.

The two methods, if they work, will represent a remarkable scaling down of Big Science, essentially putting the equivalent of a \$50 million genome-sequencing center on the desk of every researcher and physician.

The methods are giant strides toward the goal of sequencing the human genome so cheaply that it could be done routinely for medical reasons. The rallying cry for this goal is the \$1,000 genome. "The \$1,000 genome has been my passion and obsession ever since I was a graduate student," Dr. Church said.

A price tag of even \$20,000 or so, which now seems attainable in the next few years, would bring whole genome sequencing within the same range as other medical procedures.

The new sequencing methods are quite similar in approach. They load the DNA fragments to be sequenced onto ultrasmall beads and visualize the sequence of each fragment through reactions that cause the beads to light up.

A principal difference lies in the cost of the equipment. The DNA sequencing machine now being sold by 454 Life Sciences costs \$500,000. Jonathan M. Rothberg, chairman of the board, says a single machine does the job of a \$50 million sequencing center.

The Harvard machine is even cheaper. It uses "off-the-shelf instrumentation and reagents," the authors say, explaining how researchers can set up sequencing centers with mostly standard equipment.

The most expensive element is a \$140,000, computer-controlled digital microscope needed to record the color changes on a slide containing millions of DNA-carrying beads. For labs that already possess such a microscope, as many do, the equipment costs would be small. All they need do is follow the free recipe provided by Dr. Church.

Instead of using bacteria to amplify fragments of DNA by reproducing them, the Harvard method captures each fragment in a drop of liquid, which contains all the ingredients for the chemical amplification method -- the polymerase chain reaction.

The contents of each drop are loaded onto beads that are then embedded in a gel, with 14 million beads being packed into an area the size of a dime, and fluorescent chemical probes are used to indicate what the DNA sequences are.

The machine developed by 454 Life Sciences uses the same amplification method, which was developed by Devin Dressman and colleagues at the Johns Hopkins Medical Institutions in Baltimore. But the beads are made to signal their sequence by activating luciferase, the light producing enzyme in fireflies, and the flashes from each bead are recorded by a light-sensitive chip.

Dr. Church and Dr. Rothberg are enthusiastic about their own methods. Dr. Church says his method is more accurate and the equipment is far cheaper. Dr. Rothberg says his machines can sequence novel genomes whereas the Harvard method is good only for resequencing, or looking for variations in a genome of known sequence.

The first human genome to be completed, by the Human Genome Project in 2003, probably cost about \$800 million. Doing a second human genome by the traditional methods would now cost around \$20 million. The two new methods promise to be much cheaper. Dr. Rothberg says a human genome could be resequenced now by his method for \$1 million. Dr. Church estimates that he can do a human genome for \$2 million now and for \$20,000 in the future.

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